Review article

New insights in systemic lupus erythematosus: From regulatory T cells to CAR-T-cell strategies

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Systemic lupus erythematous is a heterogeneous autoimmune disease with potentially multiorgan damage. Its complex etiopathogenesis involves genetic, environmental, and hormonal factors, leading to a loss of self-tolerance with autoantibody production and immune complex formation. Given the relevance of autoreactive B lymphocytes, several therapeutic approaches have been made targeting these cells. However, the disease remains incurable, reflecting an unmet need for effective strategies. Novel therapeutic concepts have been investigated to provide more specific and sustainable disease modification compared with continued immunosuppression. Autologous hematopoietic stem cell transplantation has already provided the proof-of-concept that immunodepletion can lead to durable treatment-free remissions, albeit with significant treatment-related toxicity. In the future, chimeric antigen receptor-T-cell therapies, for example, CD19 chimeric antigen receptor-T, may provide a more effective lymphodepletion and with less toxicity than autologous hematopoietic stem cell transplantation. An emerging field is to enhance immune tolerance by exploiting the suppressive capacities of regulatory T cells, which are dysfunctional in patients with systemic lupus erythematous, and thus resemble promising candidates for adoptive cell therapy. Different approaches have been developed in this area, from polyclonal to genetically engineered regulatory T cells. In this article, we discuss the current evidence and future directions of cellular therapies for the treatment of systemic lupus erythematous, including hematopoietic stem cell transplantation and advanced regulatory T-cell–based cellular therapies. (J Allergy Clin Immunol 2022;150:1289-301.)

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Systemic lupus erythematosus (SLE) is a heterogeneous autoimmune disease, characterized by a loss of self-tolerance with autoantibody production, cellular-tissue infiltration, and end-organ damage that can potentially lead to serious organ complications and even death.[1] It affects women of child-bearing age, with a female to male ratio of about 9:1 commonly reported.[2] The overall disease prevalence ranges from 20 to 150 per 100,000, and both incidence and prevalence of SLE are continuously increasing with substantial geographical variability.[3] The mortality of the disease has continuously improved in recent years due to the improved understanding of the pathogenesis and advances in therapy, resulting in a 15-year survival of currently 85% to 95%.[4,5] Nevertheless, despite these advances, SLE is still associated with a major burden with differential impact on populations, economic costs, and health-related quality of life. Hence, there is an ongoing and unmet need for novel, disease-specific, effective and safe treatment approaches.

PATHOGENIC INSIGHTS INTO SLE

The immunopathogenesis of SLE is complex and involves genetic, environmental, hormonal, epigenetic, and immunoregulatory factors that act either sequentially or simultaneously on the immune system.[1] A clearance defect of apoptotic cells with accumulation of undigested apoptotic remnants may provoke the first hit in the break of self-tolerance by activating normally quiescent

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Abbreviations used
allo-HSCT: Allogeneic HSCT
BAAR: B-cell–targeting antibody
CAR: Chimeric antigen receptor
CYC: Cyclophosphamide
EBMT: European Society for Blood and Marrow Transplantation
FVIII: Factor VIII
GvHD: Graft-versus-host disease
HSCT: Hematopoietic stem cell transplantation
MSC: Mesenchymal stem cell
SLE: Systemic lupus erythematosus
Tconv: Conventional T
TCR: T-cell receptor
Treg: Regulatory T
T1D: Type 1 diabetes

autoreactive lymphocytes that, on repeated or chronic stimulation, may escape self-regulation.[6] Neutrophils, particularly low-density granulocytes, seem to perpetuate the complex interplay between innate and adaptive immune responses, by synthesizing increased levels of proinflammatory cytokines and forming neutrophil extracellular traps, which contain immunostimulatory proteins and autoantigens, including double-stranded DNA.[7] In addition, IFN-I signaling pathways, mimicking sustained antivirus responses, have been related to lupus disease susceptibility, and seem to contribute to the immunopathology by amplifying autoimmune responses,[8] for example, by driving autoreactive humoral activity,[9] ultimately resulting in the generation of autoreactive plasma cells and production of antinuclear antibodies.

Role of B cells

B cells contribute to the immunopathogenesis of SLE via multiple mechanisms. As progenitors of plasma cells, they are central in the generation of pathogenic autoantibodies. In addition, they mediate deleterious functions through antigen presentation to T cells, costimulatory functions via the expression of accessory molecules engaging stimulatory receptors on T cells, and the production of cytokines.[10] The marked B-cell hyperactivity in SLE is reflected by the presence of peripheral blood $CD19^{+}CD20^{-}CD27^{++}$ plasmablasts that correlate with disease activity and serum anti–double-stranded DNA autoantibody titers.[11,12] Altered B-cell subset distribution in SLE also includes the predominance of $IgD^{-}CD27^{-}$ double-negative B cells that express CD95.[13] Recent studies indicated that this B-cell subset is enriched for $CD11c^{+}Tbet^{+}$ memory B cells[14] that have been associated with autoreactivity,[15] as well as $CD19^{low}$ $CXCR5^{-}CD21^{-}$ B cells, characteristic for extrafollicular generation.[16] These memory B-cell subsets share functional properties and transcriptomic signatures with plasmablasts, suggesting their contribution to autoantibody production. In addition, B cells obtained from patients with SLE have altered expression profiles of regulatory checkpoint molecules, such as B- and T-lymphocyte attenuator (BTLA),[17] and display intrinsic abnormalities in signal transduction and immunometabolism.[18] Once activated, memory B cells differentiate into plasmablasts that subsequently migrate to the bone marrow or inflamed tissue to become long-lived memory plasma cells. In SLE, pathogenic autoantibodies are secreted from both subsets. Short-lived plasma cells are usually associated with lupus flares,[11] whereas long-lived plasma cells contribute to the disease chronicity by the continuous secretion of autoantibodies.[19]

Role of T cells

In addition to B-cell disturbances, T cells seem to be central in lupus pathology. Particularly, expanded populations of $CD4^{+}$ T follicular-helper and T peripheral helper cells facilitate B-cell activation and autoantibody production,[20,21] whereas cytotoxic T cells promote local inflammatory responses, for example, in lupus nephritis,[22] potentially contributing to tissue injury. A common feature of lupus T cells is an upregulation of interferon response genes, as recently identified in peripheral blood[23] and skin-infiltrating T cells by single-cell transcriptomics.[24] On a molecular level, a number of mechanisms, including altered expression and/or activity of protein kinases and phosphatases,[25,26] and transcription factors[27,28] are involved in the increased generation of effector T-cell phenotypes, increased expression of proinflammatory (IL-17A and IL-23) cytokines, and reduced expression of immuneregulatory cytokines (IL-2).[27] As a consequence, deficient IL-2 production contributes to reduced numbers and altered function of regulatory T (Treg) cells in SLE,[29,30] facilitates the amplification of inflammation through reduced activation-induced cell death, and plays a role in the development of secondary immune deficiency in SLE, such as reduced function of cytotoxic T cells.[31,32]

THERAPEUTIC STRATEGIES FOR SLE

Despite the era of modern biological and targeted therapies, a cure for SLE still remains elusive and approved treatments aim to provide a disease modification allowing to control symptoms and organ manifestations.[33] According to recent European League Against Rheumatism recommendations,[34] the goal of treatment is to achieve remission,[35] or where remission cannot be reached, a state of low disease activity.[36] Embedded into a treat-to-target concept, these target criteria continuously need to be monitored by validated lupus activity indices and treatment adapted accordingly.[34] Important other recommendations include avoidance of disease flares, reduction in steroid use, improvement of health-related quality of life, and prevention of accumulating organ damage. Overarching treatment principles indicate that the treatment of patients should be adapted to multiple disease-specific and patient-specific aspects, especially the individual profile of involved organ manifestations, and should be based on a shared decision.[37]

Current therapeutic concepts for SLE primarily focus on a chronic suppression of autoreactive immune responses, which may be achieved by conventional immunosuppressive or biologic disease-modifying therapies, targeting cellular or soluble components involved in lupus immunopathology. Because of the complexity of the underlying immune dysregulation in SLE, usually a multitarget therapeutic approach is required to control symptoms and halt progression.[37] Nevertheless, although providing more specificity and efficacy, these disease-modifying therapies have to be administered continuously or repeatedly, which may be associated with the cumulative risk of infectious complications or comorbidity, and are cost-effective. Alternatively, high-dose immunosuppression followed by hematopoietic stem cell transplantation (HSCT) has emerged as

an effective on/off therapy that has the capacity to provide long-term, treatment-free remissions, indicating that the resetting of the immune system by depleting autoreactive immunologic memory cells with a consecutive reinduction of immunologic self-tolerance has curative potential.[37]

Disease-modifying therapies

In addition to specific recommendations for antiphospholipid syndrome[38] and neuropsychiatric SLE,[39] the European League Against Rheumatism/American College of Rheumatology (ACR) taskforce recently updated the recommendations for the treatment of SLE[34] and lupus nephritis.[40] In terms of pharmacologic treatment, use of hydroxychloroquine is recommended for all patients at a dose not exceeding 5 mg/kg of body weight. For chronic maintenance treatment, glucocorticoids should be minimized to less than 7.5 mg/d prednisone equivalent and, if possible, withdrawn. If required, immunosuppressive drugs, such as azathioprine, methotrexate, mycophenolate mofetil, or cyclophosphamide (CYC), may be added. For patients with severe organ involvement and insufficient response to either mycophenolate mofetil or CYC, treatment with rituximab is recommended, despite negative results from randomized controlled trials. The only biologic therapy recommended with a grade A recommendation is the B-cell–activating factor–targeting mAb belimumab, which demonstrated efficacy in both renal[41] and nonrenal lupus manifestations.[42] In addition, the IFN-α receptor–targeting antibody anifrolumab was recently approved as add-on biologic therapy for SLE,[43] as well as the novel calcineurin inhibitor voclosporin for lupus nephritis.[44]

Novel therapies currently investigated in clinical phase II or III trials with promising results include Janus kinase inhibitors,[45] mAbs targeting blood dendritic cell antigen 2,[46] inhibiting the T-B-cell interaction, for example, with anti-CD40L,[47] as well as novel B-cell–directed mAbs, such as obinutuzumab (anti-CD20 mAb).[48] In addition, small pilot studies suggested beneficial clinical responses of plasma cell–depleting approaches using the proteasome inhibitor bortezomib,[49] atacicept (Transmembrane Activator and Calcium-modulator and cytophilin ligand Interactor-Ig),[50] and the CD38-targeting mAb daratumumab[23] (Fig 1).

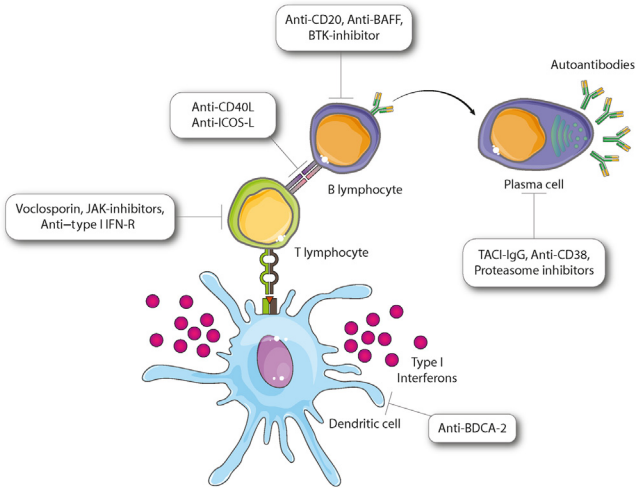

FIG 1. Novel pharmacological targets for SLE. The figure reports some of the targets and their cellular expression of novel drugs currently under evaluation in several clinical trials for SLE. *BAFF*, B-cell–activating factor; *BDCA2*, blood dendritic cell antigen 2; *BTK*, Bruton's tyrosine kinase; *ICOS-L*, inducible T-cell costimulator ligand; *JAK*, Janus kinase; *TACI*, Transmembrane Activator and Calcium-modulator and cytophilin ligand Interactor; *type I IFN-R*, type I interferon receptor.

Hematopoietic stem cell transplantation

Initially applied as salvage therapy for life-threatening SLE, autologous HSCT has evolved over the past years into a clinical option for patients with insufficient response to available standard therapies.[51,52] The basic principle of HSCT is to achieve a broad immune depletion, providing an initial "debulking" of the immunologic memory repertoire, including memory T and B lymphocytes as well as plasma cells that are usually refractory to standard immunosuppression but sensitive to conditioning treatment with anti–thymocyte globulin,[53] followed by regeneration of the hematopoietic and immune systems.[54,55]

To date, more than 300 patients have received autologous HSCT specifically for SLE. Between 1996 and 2020, 112 patients with SLE have been reported within the European Society for Blood and Marrow Transplantation (EBMT) registry (Fig 2). Pooled data from the largest 15 single-center experiences and multicenter trials with 339 patients included indicate a disease-free survival of 50% to 66% at 5 years despite discontinuation of immunosuppressive and other targeted disease-modifying therapies.[56] Notably, treatment-related mortality gradually declined from 12% in the first EBMT registry survey in 2004 to less than 5% in most recent reports between 2017 and 2019. Responding patients are usually free of clinical symptoms and may regain seronegativity for antinuclear antibodies, a state referred to as complete clinical and serologic remission "off therapy," which is rarely seen under conventional therapies.[35] Compared with continued insufficient or failed chronic immunosuppression, early use of HSCT has also the potential to protect against organ failure and toxicity-related morbidity, such as cardiovascular events, infections, and secondary malignancy, and improve quality of life.[57] According to previous EBMT recommendations, potential candidates for HSCT would reasonably include those with sustained or relapsed active British Isles Lupus Assessment Group (BILAG) category A remaining steroid dependent after at least 6 months of the best standard therapy, using mycophenolate mofetil or CYC with or without mAbs, with documented evidence of visceral involvement or refractory SLE.[58,59]

Allogeneic HSCT (allo-HSCT) can be used to restore a dysfunctional immune system, although its wide application has been limited by the risk of graft-versus-host disease (GvHD) and other complications connected to the procedure. Although rare, a retrospective analysis of the EBMT registry published in 2019 reported 5 patients with SLE (2 pediatrics and 3 adults) successfully treated with allo-HSCT[60] and 3 additional SLE cases in literature achieved a complete remission of autoimmune manifestations after allo-HSCT.[61-63] These observations, together with "coincidental" cases of autoimmune diseases in patients undergoing allo-HSCT for hematological malignancies and *in vivo* experiments in mouse models, suggested a potential connection between donor alloreactivity and autoimmune remission, thus suggesting the concept of a putative graft-versus-autoimmunity effect.[56,64,65]

Collectively, these evidences provide the principle for the use of allo-HSCT as a potential curative approach. Although unlikely to be used widely due to the connected side effects, occasional and

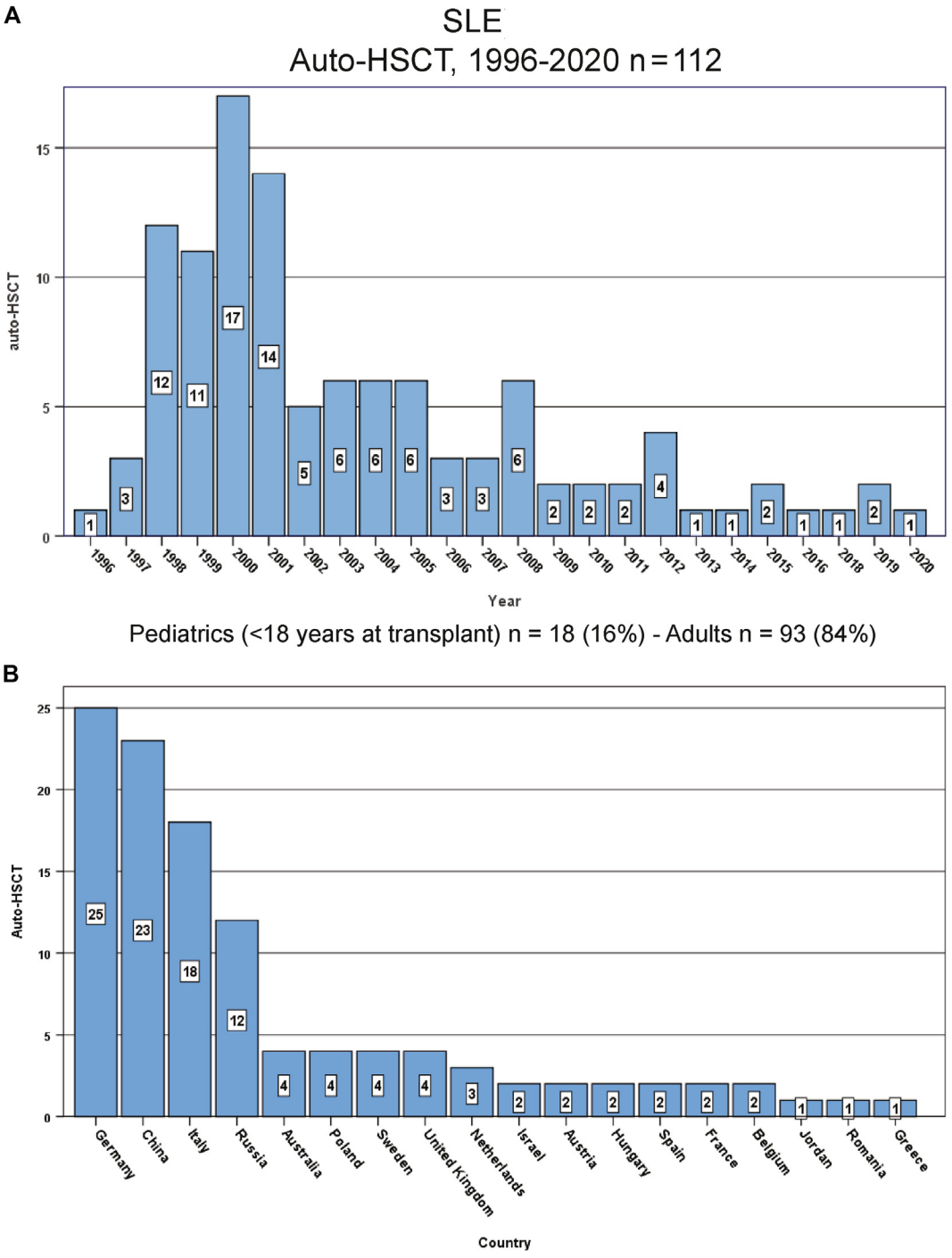

FIG 2. Number of HSCTs for SLE. **A,** The frequency of autologous HSCTs for SLE from 1996 to 2020 included in the EBMT registry. The overall number of pediatric and adult patients is reported. **B,** The number of HSCTs for SLE by country from 1996 to 2020. *Auto-HSCT,* Autologous HSCT.

carefully selected patients may be considered, especially where HSCT risks are lower, potentially with well-matched donors and improvements in allogeneic transplant technique (such as post-transplant CYC and personalized/reduced-toxicity conditioning regimens).[56]

Chimeric antigen receptor-T cells

Immunotherapy is a promising approach for the depletion of autoreactive cells. Chimeric antigen receptor (CAR)-T cells represent one of the most valuable approaches considering the encouraging results already achieved in other fields.

CARs are chimeric molecules capable of redirecting the specificity of transduced cells against a target antigen. CARs are composed of 2 major components: the extracellular domain and the intracellular portion. The extracellular domain accounts for the recognition of the target and in most of the cases derives from both the light and the heavy chain of the variable portion of mAb, linked together (single-chain variable fragment).[66-68] The intracellular portion mediates the transduction of the signal on antigen binding, and it is composed of 1 or more signaling domain according to the pathway that must be engaged.[69] These 2 portions are connected together by a linker peptide or spacer.[70,71]

CARs have been widely studied in the context of cancer. Several commercial and academic autologous CAR-T-cell products targeting B-cell surface antigen CD19 have been approved for B-cell malignancies and multiple myeloma.[72]

Autoreactive B cells have long been a target for SLE therapy. However, although providing clinical benefit, anti-CD20 mAbs failed to achieve the primary end points in randomized controlled trials. An anti-CD19 CAR-T-cell approach may induce a more robust B-cell depletion compared with the use of B-cell–targeting mAbs (eg, rituximab), especially in tissues in which engineered cells may access more easily. Recently, first data on the use of an anti-CD19 CAR-T-cell strategy in a patient with refractory SLE demonstrated a rapid clinical remission without notable adverse effects, accompanied by sustained depletion of circulating B cells and a rapid disappearance of serum anti–double-stranded DNA antibodies.[73] Subsequently, the same group treated an additional 4 patients with SLE with a refractory disease course. Preliminary results on safety and efficacy are encouraging, but data on long-term follow up are warranted.[74] This first clinical experience builds on preclinical work in mouse models, demonstrating the potential of CAR-T cells to ablate autoantibodies and $CD19^+$ B cells, thus improving disease manifestations.[75]

Toxicities, including cytokine-release syndrome and neurologic toxicities, are important side effects associated with CAR-T cells.[72] These side effects depend on multiple factors, including CAR design, and can be solved using specific strategies.[76] B-cell aplasia is another well-established consequence of anti-CD19 CAR-T cells, which can last until T cells are functional.[77] In SLE, the depletion of B cells represents a potential curative approach but might increase the susceptibility to infections.

Collectively, CAR-T cells represent an interesting and promising approach for SLE. Preliminary data are encouraging with convincing efficacy and a favorable safety profile. However, open questions remain, particularly the durability of responses during B-cell repopulation and the identification of an appropriate target population.

TREG CELLS

Treg cells are a specialized branch of $CD4^+$ T lymphocytes endowed with suppressive functions, which maintain the immune tolerance and prevent autoimmunity.[78] They represent a very heterogeneous population, distributed in secondary lymphoid organs and tissues, phenotypically hardly distinguishable from their conventional counterparts. Treg cells constitutionally express high levels of the IL-2 receptor alpha (CD25), and they are highly enriched in the fraction of $CD4^+CD25^{bright}$ cells. In addition, they are classically identified as $CD127^{low}$ and Forkhead box $P3^+$ cells. However, none of these markers is uniquely expressed by Treg cells, but may also be present on activated conventional T (Tconv) cells.[79] The Forkhead box P3 transcription factor is essential for Treg-cell development, and its absence causes a severe genetic disease with autoimmune manifestations.[80,81] Other markers have been described in literature, often associated with highly suppressive Treg-cell subsets.[82,83]

Treg cells are endowed with immune-suppressive functions and are able to control the activation of the immune system. Treg-cell lymphocytes can use different strategies to restrain the activity of immune cells, which can be divided into direct mechanisms, based on cell-to-cell contact, and indirect mechanisms, mediated by third-party molecules or cells.[84] Their immune suppression is broad and involves multiple components of the immune system. Treg cells suppress T and B lymphocytes via direct and indirect mechanisms. Dendritic cells represent another target, which can be reprogrammed toward an immune-suppressive phenotype (tolerogenic dendritic cells), thus limiting the activation of the adaptive immunity.[85] Treg-cell activity can also involve monocytes, neutrophils, and natural killer cells.[86]

Treg-cell dysfunctionality in SLE

Several studies investigated the role of Treg cells in SLE, obtaining contradictory results. In 2019, a meta-analysis evaluated 18 published studies about Treg cells in lupus, including a total of 628 patients and 601 healthy controls. Despite a great heterogeneity in the methodology, pooled data indicated a reduction in circulating Treg cells in patients with active SLE. In terms of functionality, Li et al[29] reported 3 publications in their meta-analysis: 2 studies showed reduced Treg-cell–suppressive functions in SLE, whereas the third one did not identify any significant difference. Pooled data did not reveal any functional difference between patients and controls. Treg-cell selection, the SLE classification criteria that were used, and different experimental methods might explain this great heterogeneity.[29]

In 2013, Alexander et al[87] reported a selective and unique expansion of Forkhead box $P3^+$ $Helios^+$ Treg cells in patients with SLE compared with both healthy subjects and patients with other autoimmune diseases. These cells were highly proliferative and suppressive and displayed an effector memory phenotype and a restricted T-cell receptor (TCR) repertoire, probably representing a compensatory mechanism to control autoreactive cells in tissues.[87]

Collectively, the role of Treg cells in SLE pathogenesis is still controversial. The development of autoimmune manifestations requires the breakdown of the immune tolerance, which is preserved by Treg cells, but up to now it is unclear whether this could be due to a Treg-cell defect in terms of numbers and/or functionality. Heterogeneity among studies did not help to define this aspect. A harmonization of methods might lead to new insights.

TREG-CELL–BASED THERAPIES

The restoration of the immune tolerance with consequent resolution of the inflammatory response against self-antigens is one of the goals of the treatment of autoimmune diseases. Considering their properties, Treg cells represent the ideal candidate for this kind of therapeutic approach. To this end, several strategies have been developed to enhance the Treg-cell response in SLE.[88,89]

In vivo induction of Treg cells

Immunosuppressive drugs. The first approach to therapeutically use Treg cells relies on the induction of Treg cells directly *in vivo*, by enhancing their activity and/or persistence. Several drugs used for the treatment of autoimmune diseases can act directly or indirectly on Treg-cell numbers and/or functionality. For example, rapamycin/sirolimus increases the number of Treg cells through the inhibition of the mechanistic target of rapamycin (mTOR) pathway. Sirolimus has been used in several clinical trials alone or in combination with other drugs, proving effective in ameliorating the disease activity. In 2020, 1 meta-analysis of 5 studies involving 149 patients with SLE reported a significant reduction in prednisone dose, and a general improvement in the disease from both a clinical and biochemical point of view.[90]

Steroids have a role in inducing Treg cells acting on the miR-342-3p–mTOR complex 2 axis. In particular, Kim et al[91] demonstrated that Treg cells were essential in mediating the anti-inflammatory properties of dexamethasone in a mouse model of autoimmunity and that their absence completely abrogated its therapeutic activity.

Another approach relies on the indirect boost of Treg-cell expansion. This is the case of CYC used after haploidentical HSCT for the prevention of GvHD. In this context, CYC preferentially depletes proliferating conventional effector T cells due to their low expression of aldehyde dehydrogenase, the enzyme required for its degradation, which, in contrast, is expressed at significantly higher levels by Treg cells and hematopoietic stem cells. This approach proved very effective in reducing the risk of GvHD related to haplo-HSCT by favoring Treg-cell reconstitution and restoring the Treg-cell/Tconv-cell ratio.[92]

Mesenchymal stem cells. Mesenchymal stem cells represent a subset of cells endowed with immunosuppressive properties, capable of inducing Treg cells and in promoting Tconv-cell differentiation toward a T_H2 phenotype *in vitro* and *in vivo* in several preclinical models. For their properties, several clinical trials used mesenchymal stem cells in patients with SLE. Although mesenchymal stem cells have a good safety profile, their administration showed controversial results in controlling disease manifestations and their efficacy has to be assessed yet.[93]

IL-2 and muteins. Administration of IL-2, an essential cytokine for Treg-cell growth and survival, may enhance immune regulation. Patients with SLE and lupus-prone mouse models showed an impairment of the IL-2 production, potentially explaining the Treg-cell defect in this condition.[94] The administration of IL-2 in lupus-prone mice improved the number of circulating Treg cells and the disease severity.[95]

In humans, after the first successful open-label trial in SLE,[30] several studies indicated a beneficial effect of low-dose IL-2 alone or in combination with the standard of care in improving disease activity, ameliorating disease manifestations, reducing autoantibodies, and complement consumption.[96] In addition, low-dose IL-2 increased the number of circulating Treg cells and their proliferative capacity, together with a concomitant reduction in follicular-helper T cells, T_H17 $CD4^+$ lymphocytes, and memory B cells.[97]

Low-dose IL-2 administration displayed a good safety profile. The described adverse events were very few, mild, and transient, principally constituted by local reaction at the injection site. In a minority of patients, fever and influenza-like symptoms were reported but they were transient and mild and did not require specific treatments.[98]

Concerns about IL-2 administration regard its poor pharmacodynamics with frequent and long-term administration, with the risk of expanding Tconv cells, worsening autoimmune manifestations. For this reason, several mutated IL-2 variants (called muteins) have been developed to selectively bind the high-affinity IL-2 receptor that is preferentially expressed by Treg cells, thus enhancing their immunomodulatory properties.[99] Clinical trials are now ongoing to evaluate their efficacy.[100]

A list of clinical trials with adoptive Treg-cell therapy with IL-2 is summarized in Table I.

Different compounds proved effective in boosting Treg-cell expansion *in vivo*, albeit with different efficacy. Classic immunosuppressive drugs are very well known, and they typically can control disease flares but with frequent relapses after their discontinuation. Mesenchymal stem cells showed a good safety profile in several clinical trials but a limited efficacy achieving contradictory results. The difference in the administered dose might explain the discrepancies observed between the preclinical studies and clinical trials in humans.

The administration of low-dose IL-2 and muteins represents a potential novel approach for increasing Treg-cell survival and boosting their suppressive properties, potentially helping to restore the immune tolerance. Several clinical trials showed encouraging results in terms of both efficacy and safety profile. Further studies are required to optimize this approach.

Adoptive transfer of polyclonal Treg cells

A more direct approach is based on the *in vitro* expansion of Treg cells and their subsequent reinfusion. In the last 3 decades, the adoptive cell transfer has progressively emerged as a novel strategy for the treatment of several conditions, in particular for cancer and infectious diseases. In the context of autoimmunity, Treg cells represent ideal candidates for an adoptive transfer due to their abilities to control the activation of the immune system.[88,89]

Treg cells were used in 3 major contexts: autoimmune diseases, treatment of GvHD, and transplant rejection after solid-organ transplantation. For SLE, the only clinical report regarding adoptive Treg-cell therapy dates back to 2019. Dall'Era et al[104] reported a patient with active cutaneous SLE treated with 10^8 polyclonal Treg cells, which had been expanded *ex vivo* and labeled with deuterium. After 4 weeks, a marked amelioration of the skin lesions was reported despite reduction of labeled Treg cells in peripheral blood. Skin biopsy revealed an enrichment of Treg cells and IL-17–producing $CD4^+$ and $CD8^+$ cells and a reduction in IFN-γ–secreting T cells.[104]

Most clinical trials with adoptive Treg-cell therapy for autoimmune diseases have been performed for the treatment of type 1 diabetes (T1D). In 2014, Marek-Trzonkowska et al[105] conducted a phase I trial in 12 patients with T1D using autologous polyclonal Treg cells, and demonstrated a clinically significant benefit, with 8 subjects achieving clinical remission, with 2 of them becoming insulin-independent. Similar results have been obtained in a subsequent phase I trial in 2015, including 15 patients with T1D treated with polyclonal autologous Treg

TABLE I. Summary of studies with low-dose IL-2 in SLE

No. of patients	Groups	Therapy	Outcomes	Reference
1	IL-2 + SOC	1. 5-3.0 MU/d IL-2 s.c. for 5 d/cycle for 4 cycles (9-16 d between cycles)	Increase in circulating Treg cells during cycles. Improvement in SLEDAI, decrease in immune- suppressive therapy, no new manifestations, decrease in anti-DNA antibodies. No SAE, mild local reactions, transient fever	Humrich et al,[101] 2015
5	IL-2 + SOC	1.5 MU/d for 5 d (1 cycle only)	Increase in circulating Treg cells and Treg-cell–associated markers. Increase in Treg-cell/Tcovn-cell proliferation ratio. Increased proliferation of Tconv cells and NK cells but stable counts	von Spee-Mayer et al,[30] 2016
38	IL-2 + SOC	1 MU every other day for 2 wk/cycle for 3 cycles (14 d between cycles)	Increase in Treg cells and Treg-cell suppression. Reduction in Tfh and T_H17 $CD4^+$ Tconv cells. Improvement in SRI-4, amelioration of symptoms, increase in complement, reduction in anti-DNA antibodies and proteinuria. No SAE, mild local reactions, influenza-like symptoms	He et al,[96] 2016
12	IL-2 + SOC	0.75-3.0 MU/d IL-2 s.c. for 5 d/cycle for 4 cycles (9-16 d between cycles)	Increase in circulating Treg cells and Treg-cell–associated markers. Increase in Treg-cell/Tcovn-cell proliferation ratio. Increased proliferation of $CD8^+$ Tconv cells and NK cells. Reduction in Tfh Tconv cells. Reduction in circulating B cells. Improvement in SLEDAI, amelioration of symptoms, increase in complement, reduction in anti-DNA antibodies. No SAE, mild local reactions, influenza-like symptoms. Transient increase in acute-phase proteins	Humrich et al,[97] 2019
30	18 patients IL-2 + SOC and 12 patients SOC	1 MU every other day for 2 wk/cycle for 3 cycles (14 d between cycles)	Increase in Treg cells during cycles. Higher remission rate in the IL-2 group at 10 wk, improved renal outcomes. No SAE, mild local reactions, influenza-like symptoms, nausea, diarrhea	Shao et al,[102] 2019
50	IL-2 + rapamycin	100 WU 3-5 d/mo + rapamycin 0.5 mg every other day for 24 wk	Increase in Treg cells during cycles. Reduced T_H17 Tconv-cell/ Treg-cell ratio. Improvement in SLEDAI, decrease in immune-suppressive therapy. No SAE	Zhao et al,[103] 2019
60	30 patients IL-2 + SOC and 30 patients placebo + SOC	1 MU every other day for 2 wk/cycle for 3 cycles (14 d between cycles)	Increase in Treg cells and NK cells in the IL-2 group. Improvement in SRI-4, amelioration of symptoms, higher remission rate of lupus nephritis, increase in complement, reduction in anti-DNA antibodies in the IL-2 group. No SAE, mild local reactions, influenza-like symptoms	He et al,[98] 2020

The table reports the most relevant studies regarding low-dose IL-2 in patients with SLE, describing the number of enrolled patients, groups of treatment, the schedule of administration, a brief description of the outcome, and the bibliographic reference.
NK, Natural killer; *SAE*, serious adverse events; *s.c.*, subcutaneously; *SLEDAI*, Systemic Lupus Erythematosus Disease Activity Index; *SOC*, standard of care; *Tfh*, T follicular-helper.

cells (cell dose: 0.05 $\times$ 10^8 to 26 $\times 10^8$ cells/patient). Deuterium-prelabeled cells were detectable from the first day of infusion, peaking at 7 to 14 days and reducing by 75% of the initial dose after 3 months, while after 1 year, Treg cells were detectable only in 4 patients.[106] More comprehensive analyses of polyclonal Treg-cell clinical trials have been published elsewhere.[107,108]

Although the experience in SLE is limited, data on adoptive polyclonal Treg-cell transfer in autoimmunity collectively proved feasibility and safety, albeit with only moderate efficacy. This may be explained by the low level of Treg-cell persistence *in vivo* at least in peripheral blood and the limited number of disease-relevant antigen-specific cells in the final cell product. In fact, as suggested by mouse studies, antigen-specific cells are superior than polyclonal Treg cells in controlling autoimmune responses.[89,109] The direct expansion of adequate numbers of antigen-specific Treg cells is cumbersome and greatly limits the development of efficacious adoptive Treg-cell therapies. The advent of genome editing techniques allowing the generation of high numbers of antigen-specific Treg cells greatly boosted this field.

Genetically engineered Treg cells

Modern techniques for efficient genome editing allows the generation of engineered T cells. So far, the major field of application of these approaches is represented by cancer, where genome editing has been largely used to redirect T-cell specificity and increase their potency and/or their safety profile.

However, genome editing can also be used in the context of autoimmunity to increase the number of disease-relevant antigen-specific regulatory cells. In particular, 2 different strategies have been developed: TCR-redirected regulatory cells and CAR-Treg cells.

TCR-redirected Treg cells

The first TCR gene transfer approach was already reported in the nineties by Clay et al,[110] who efficiently transduced human T cells with a melanoma-specific TCR using a retroviral vector, and the first study with engineered TCRs in cancer was published in 2006.[111] Subsequently, several other TCRs have been identified in cancer.[69]

Preclinical studies demonstrated the feasibility and the efficacy of TCR gene transfer for the treatment of autoimmune diseases, especially for T1D. In addition, Brusko et al[112] redirected Treg-cell specificity using an antityrosinase TCR, specifically a melanoma antigen. The authors demonstrated the feasibility of the process and the capacity of engineered Treg cells to respond, expand, and exert suppressive capacities in the presence of the cognate antigen.[112]

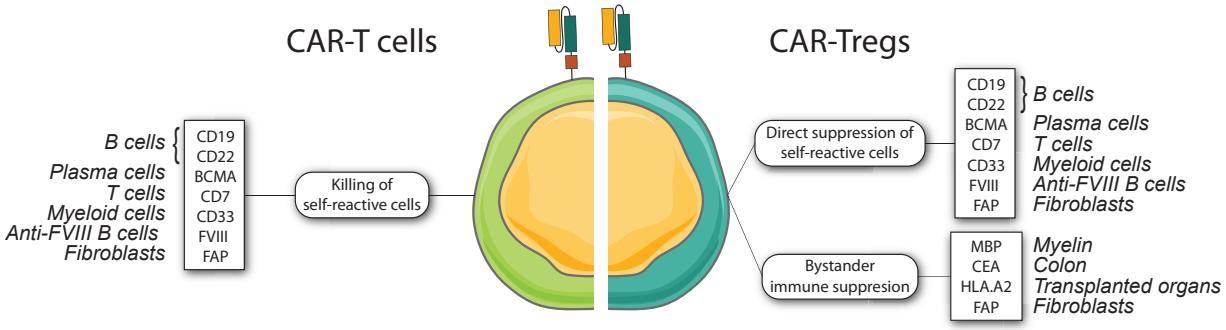

FIG 3. CAR-T-cell strategies comparison. A comparison between conventional CAR-T cells and CAR-Treg cells is reported with a list of the most-studied targets. For each molecule, the associated cellular target is also reported. In addition, for each target, the therapeutic strategy is provided. CAR-T cells can be used to selectively deplete target components relevant for the autoreactive process. CAR-Treg cells can control the autoimmune process by exerting an immune-regulatory activity. Two different strategies can be adopted with CAR-Treg cells: a direct suppression of target cells through a cell-to-cell contact or a broader locoregional immune suppression, especially localized in target organs. *BCMA*, B-cell maturation antigen; *CEA*, carcino-embryonic antigen; *FAP*, fibroblast activation protein; *MBP*, myelin basic protein.

TABLE II. Summary of active clinical trials with CAR-Treg cells

Disease	Target	Starting date	Identifier	Study design	End points
Renal transplantation	HLA-A2	March 2021	NCT04817774	Phase I/IIa multicenter open-label trial	Safety and tolerability Prevention of rejection
Liver transplantation	HLA-A2	January 2022	NCT05234190	Phase I/IIa multicenter open-label trial	Safety and tolerability Prevention of rejection Immunosuppressive withdrawal
R/R $CD19^+$ B-ALL	CD19	November 2022	NCT05114837	Phase I/IIa single-center open-label trial	Safety and tolerability Antitumor efficacy

The table reports a list of actively recruiting clinical trials with CAR-Treg cells updated to June 2022. The underlying condition, the CAR target, the starting date, the trial identifier, the study design, and the declared primary and secondary end points are reported. Active CAR-Treg-cell clinical trials are found on www.clinicatrials.gov.
R/R $CD19^+$ B-ALL, Refractory/relapsing $CD19^+$ B-acute lymphoblastic leukemia.

In 2017, 2 publications reported the development of islet-specific TCR-redirected Treg cells. Yeh et al[113] isolated an anti–glutamic acid decarboxylase TCR and generated anti–glutamic acid decarboxylase Treg cells, which controlled *in vitro* the proliferation of anti–glutamic acid decarboxylase Tconv cells. Hull et al[114] cloned 2 TCRs, specific for tyrosine phosphatase (IA2) and insulin, respectively. TCR-redirected Treg cells showed antigen-specific immune-suppressive capacities *in vitro*.

Kim et al reported the efficacy of TCR-redirected Treg cells in 2 other contexts. Anti–factor VIII (FVIII) Treg cells prevented the immunization against recombinant FVIII in hemophilia.[115] In 2018, the same group showed the feasibility of the same approach in the context of central nervous system inflammation. They generated anti-MBP Treg cells, which displayed antigen-specific immune-suppressive capacities *in vitro* and *in vivo* in a mouse model of experimental autoimmune encephalitis.[116]

CAR-Treg cells

CARs represent a potential solution to redirect Treg-cell specificity, and several preclinical studies proved the efficacy of CAR-Treg cells in autoimmunity. In 2009, Hombach et al[117] generated anti–carcinoembryonic antigen CAR-Treg cells and demonstrated that these cells inhibited carcinoembryonic $antigen^+$ tumor rejection by antigen-specific Tconv cells.[117] Lee et al[118] obtained similar results in a model of $CD19^+$ acute B-cell leukemia, showing how anti-CD19 CAR-Treg cells in the tumor site abrogated the activity of conventional anti-CD19 CAR-T cells. In 2020, Imura et al[119] demonstrated the efficacy of anti-CD19 CAR-Treg cells in controlling B-cell proliferation and antibody production *in vitro* and in reducing the risk of developing GvHD in a xenograft mouse model.

In 2016, MacDonald et al[120] generated anti–HLA-A02 CAR-Treg cells. They showed that engineered lymphocytes displayed antigen-specific suppressive properties *in vitro* and prevented xenograft GvHD induced by $HLA\text{-}A2^+$ PBMCs *in vivo*. In 2017, 2 groups confirmed these results in xenograft mouse models, demonstrating that anti–HLA-A02 CAR-Treg cells blocked the rejection of transplanted human skin.[121,122]

Scott's group used CAR-Treg cells for the prevention of immune responses against recombinant FVIII in hemophilia. In 2017, Yoon et al[123] generated anti-FVIII CAR-Treg cells that blocked FVIII-specific Tconv-cell responses and suppressed the generation of anti-FVIII antibodies both *in vitro* and *in vivo*. Subsequently, in 2018, the same group generated a BAAR, a B-cell–targeting antibody, a novel strategy to selectively block anti-FVIII

B cells, demonstrating how BAAR-Treg cells retained their suppressive capacities and blocked anti-FVIII antibody production both *in vitro* and *in vivo*[124] (Fig 3). Considering these promising results, first clinical trials involving CAR-Treg cells have been developed, from which one is already enrolling patients, whereas others are expected to start in the next months. An updated list of trials as of June 2022 is depicted in Table II.

Collectively, several preclinical studies demonstrated the feasibility and functionality of engineered Treg cells. TCRs and CARs represent 2 different strategies, both effective in redirecting Treg-cell–suppressive capacities in an antigen-specific manner, although none of them has been specifically used in SLE. TCRs and CARs have some differences, and the choice of one or the other approach depends on the target antigen. TCRs can recognize both extracellular and intracellular antigens but are MHC-restricted. CARs are limited to extracellular molecule but are MHC-independent.[88] Engineered Treg cells can exert their suppressive functions directly acting on self-reactive cells. In addition, they can exert a locoregional immunosuppression by targeting an antigen expressed in specific tissues to control locally the inflammatory response,[84] as in the case of anti-MBP engineered Treg cells.[116]

Given the complex pathogenesis of SLE with autoreactive responses against multiple self-antigens, the identification of a potential target for an adoptive Treg-cell therapy remains a therapeutic challenge. CARs specific for molecules expressed by pathogenic cells, such as CD19 for B cells[73] or B-cell maturation antigen for plasma cells,[125] represent a possible solution. However, these targets are poorly specific for autoreactive cells, being expressed also by their protective counterparts.

BAARs could increase the specificity: these molecules can selectively target self-reactive B lymphocytes and in SLE they might target pathogenic cells.[124] Finally, for selective applications, locoregional immune suppression might represent a solution, like anti-MBP for neurologic manifestations.[116]

In conclusion, the identification of a specific target for SLE is still cumbersome. TCRs and CARs are 2 complementary approaches with specific characteristics. Alternative strategies may be used with already available molecules, especially in specific situations. Some suggestions are reported in Fig 3.

CONCLUSIONS AND FUTURE DIRECTIONS

SLE is a complex disease characterized by a breakdown of the immunologic self-tolerance.[1] Autoreactive B and T cells, in conjunction with key players of the innate immune system, play a central role in the disease pathogenesis.[10,21] Several therapeutic approaches have been attempted so far, many of them with promising results, yielding a therapeutic concept of disease modification that controls symptoms and halts progression but provides no curative potential.[37] New insights into SLE pathogenesis have led to the development of more specific drugs, in particular mAbs, which specifically target disease-relevant molecules.[41] Nevertheless, targeted biologic therapies usually require continuous administration to control disease manifestations, and may be associated with the cumulative risk of infections and comorbidity.

A barrier for long-term remissions represents the autoreactive immunologic memory, which is usually formed long before symptoms of the disease occur, and which is mostly refractory to available biologic therapies, particularly autoantibody-secreting memory plasma cells.[19] To control self-reactive cells, in particular memory ones, 2 different approaches have been developed: the first one relies on eliminating autoreactive immune cells (immunoablation), and the second one aims at restoring the immune tolerance (immune regulation).

To obtain the immunoablation of self-reactive cells, autologous HSCT (and rarely allogeneic HSCT) has been used in patients with SLE and already provided the proof-of-concept that long-term remissions can be achieved after resetting the immune system into a self-tolerant state. However, autologous HSCT can be associated with considerable transplant-related mortality and other long-term complications, such as secondary autoimmune diseases.[57] Furthermore, it remains unclear what particular components of the memory compartment need to be targeted and how deep the lymphocyte lineage depletion will be required to achieve sustainable responses in SLE. In this regard, it will be of interest to follow the results of ongoing CD19 CAR-T-cell therapies in SLE.[73,75] Compared with mAbs, this strategy has the advantage of a broader depletion of autoreactive B cells, especially those maintained in inflamed tissues. First results already indicate that this approach provided a therapeutically relevant depletion of B cells along with significant reductions in autoantibodies. However, whether such deep B-cell lineage depletion is sufficient to induce durable responses, or further memory compartments, such as CD19-negative plasma cells or T cells, to be target in addition remains unclear.

Another therapeutic option to control chronic autoimmune responses in SLE is to foster immune regulation, aiming at restoring the immune tolerance. Considering the central role of Treg cells in maintaining self-tolerance, they represent the ideal candidate for such a kind of approach. Several therapeutic approaches are under investigation, either directly "fueling" Treg cells *in vivo*, for example, with IL-2 or muteins,[30,96,100] or by *ex vivo* manipulation followed by a subsequent Treg-cell reinfusion (Fig 4). Clinical trials of adoptive Treg-cell therapies demonstrated feasibility and a proof of efficacy. However, the use of polyclonal Treg cells achieved only modest and transient clinical results, probably due to a low number of disease-relevant Treg cells in the cell product or due to a reduced persistence *in vivo*.[109] New strategies rely on the use of engineered regulatory cells, which represent a possible solution to overcome these limitations.[89]

One of the greatest limitations to the use of engineered cells is represented by the cost of the procedure, thus probably limiting its applicability to selected patients.[126] Specific criteria should be identified to select those patients eligible for an adoptive cell therapy. As for CD19 CAR-T-cell therapies, potential candidates are those with persistent and progressive disease, despite conventional or biologic therapies. In addition, specific biomarkers, for example, those related to IL-2 deficiency, may be helpful for patient selection. Some candidate biomarkers have been reviewed elsewhere.[127]

Beside the costs, manufacturing is another limiting factor for the widespread use of adoptive cell therapy. Nevertheless, the CAR-T experience in cancer revolutionized the field, increasing the availability of both academic and commercial products. Hopefully in the future, availability and costs of manufacturing facilities will gradually improve, especially with the development of decentralized units for the production of the cells.[128,129]

Safety is another key aspect of adoptive T-cell therapy, especially in the context of autoimmunity, given the chronicity of the condition compared with a life-threatening disease such as

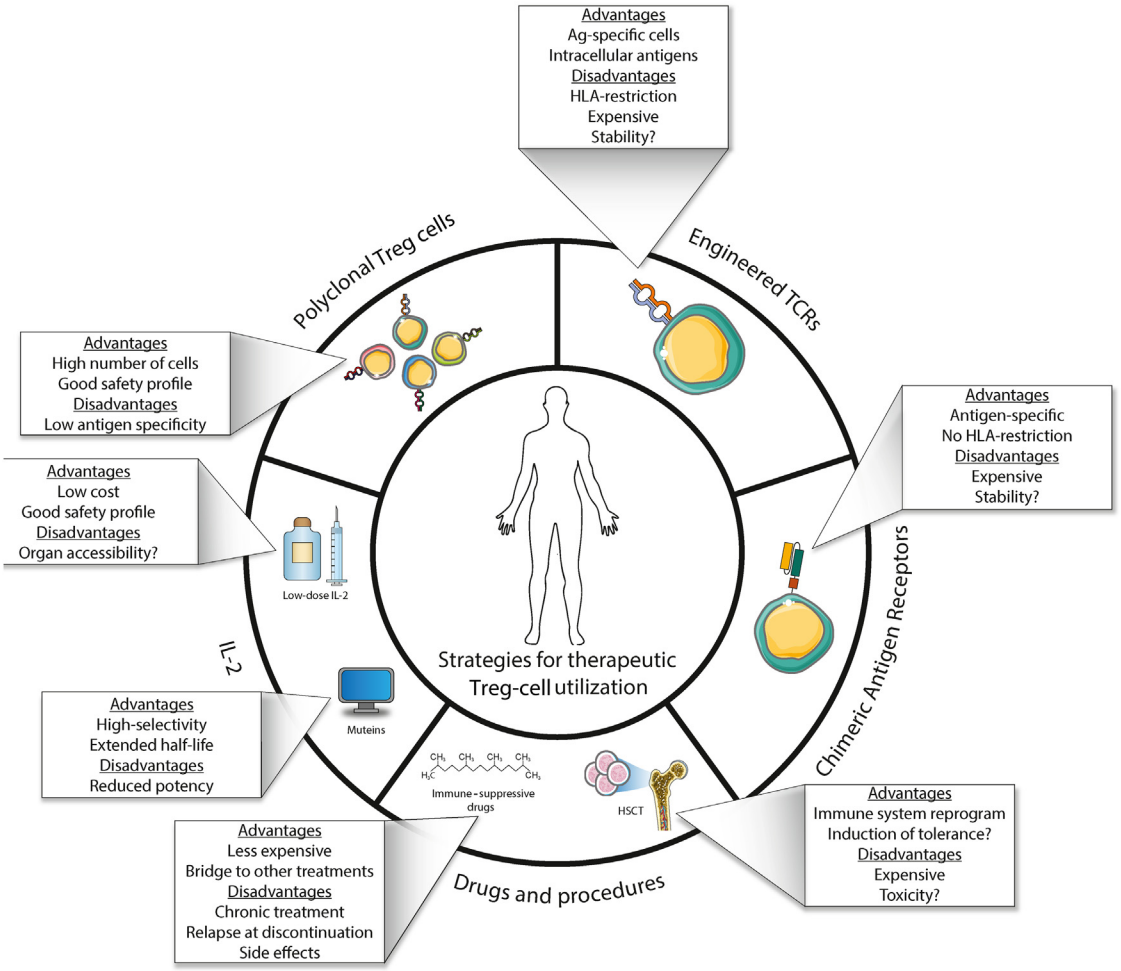

FIG 4. Summary of novel therapeutic approaches for SLE. The figure illustrates novel therapeutic fields for SLE with their advantages and disadvantages. In particular, the use of adoptive Treg-cell therapy is described as either polyclonal or engineered Treg cells. CARs and engineered TCRs can be used to generate engineered Treg cells. To increase Treg-cell activity, low-dose IL-2 and muteins are reported. Finally, the use of immunomodulatory approaches such as immune-suppressive drugs or HSCT is illustrated.

cancer. Conventional CAR-T cells have several well-established side effects in cancer,[130] whose incidence in SLE has to be addressed in future clinical trials. Regarding Treg cells, several articles demonstrated their instability in chronic inflammatory environments with their reprogramming toward conventional effector cells.[131] Addressing this issue is crucial, especially with CAR-Treg cells, where the reprogramming of the engineered lymphocytes to proinflammatory cells might worsen the underlying condition.

Collectively, SLE treatment is rapidly evolving and new approaches are currently under investigation. Better understanding of the pathologic mechanisms and recent advances in cell manufacturing have generated the development of new, specific therapies to fundamentally modify the cellular interactions and clinical outcomes. The precise role of novel cellular therapies in the future treatment algorithm of SLE remains to be determined. According to current guidelines, SLE therapies should be embedded into a concept of *disease modification* that "requires minimizing disease activity with the fewest treatment-associated toxicity and slowing or preventing organ damage progression."[33] In this regard, available therapies suppressing immune reactions with or without the use of biologic drugs are sufficient to achieve fundamental treatment goals in most patients with SLE. Therefore, in the near future, application of novel cellular therapies will still be restricted to patients with high risk for mortality or disease progression. According to recent data, such patients are reasonably those "not at target," that is, not achieving lupus low disease activity, who have a significantly increased risk of mortality, accumulating organ damage, and poor quality of life.[132]

Accumulating data from clinical trials or single experiences with HSCT or CAR T-cell therapies already demonstrated that a vast immune depletion as "on-off" therapy may provide durable responses. These promising data may set a scene for a future ambitious treatment goal of achieving therapy-free long remissions, which could become realistic in the future. Likewise, data from novel Treg-cell–based therapies providing a concept of *immune modulation* are promising and may have a

future role in providing clinical remission with low toxicity. In the future, more data are required to evaluate the risk-benefit ratio of individual novel cellular therapies, and most importantly to identify patients who will benefit most from such therapies.

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